RESPIRATORY MEDICINE

Capsaicin inhalation test for identification of sensory hyperreactivity

Å. JOHANSSON*, O. LÖWHAGEN†, E. MILLQVIST† AND M. BENDE*

*Allergy Centre, Central Hospital, Skövde, Sweden and †Asthma and Allergy Research Group, Sahlgrenska University Hospital, Gothenburg, Sweden

Abstract *Background*: Patients with upper and lower airway symptoms and with pronounced sensitivity to chemical odours, such as perfumes, flower scents and tobacco smoke, have been suggested to have sensory hyperreactivity (SHR). The symptoms have been difficult to identify with physiological measurements and the effects of various medications are doubtful. However, these patients have been found to be more sensitive to inhalation of capsaicin than healthy people. The aim of this study was to establish limit values with the capsaicin inhalation test in patients with SHR. *Methods*: Ninety-five consecutive patients with upper and lower airway problems, who were admitted for allergy testing, underwent a capsaicin inhalation test with three different concentrations. The number of coughs was registered during each challenge. Score systems were used for symptoms and influence on social life of sensitivity to odours. In relation to scored symptoms, the patients were grouped as SHR or not, and compared with 73 healthy controls. *Results*: All patients and controls coughed on capsaicin in a dose-dependent manner. Symptom score of odour sensitivity in patients was positively correlated to the response of the test. Out of 95 patients, 15 (16%) were scored to SHR. Patients with SHR reacted more to the capsaicin inhalation test than the other patients and the healthy controls. The limit values for a positive capsaicin inhalation test for the SHR were determined to be 10, 35 and 55 coughs at 0.4, 2.0 and 10 μM capsaicin, respectively. *Conclusion*: The capsaicin inhalation test well reflects the degree of airway sensitivity to chemicals and to what extent the social life is influenced. The cut-off values of the test can distinguish patients with pronounced sensitivity to odours.

doi:10.1053/rmed.2002.1340, available online at http://www.idealibrary.com on IDEAL®

Keywords capsaicin; cough; sensory hyperreactivity; multiple chemical sensitivity.

INTRODUCTION

In daily clinical work at our Allergy Centre, we see patients with symptoms that do not fit the common diagnoses. One group of such patients with upper and lower airway complaints has pronounced sensitivity to various odours such as perfumes, cleaning agents, flower scents, car exhaust fumes and tobacco smoke. These patients often have difficulty describing their symptoms, the most common being 'heavy breathing', 'difficult in getting air', 'pressure across the chest' and 'blocked nose'. When lower airway symptoms predominate, the term 'asthma-like' has been used, but a main feature among those patients is the absence of bronchial obstruction (1). The symptoms have been difficult to identify with physiological measurements and the effects of various medications are small or doubtful. The suggested mechanism behind these symptoms is a sensory hyperreactivity (SHR) (1). SHR has a strong resemblance to multiple chemical sensitivity (MCS), the term used in American literature, which features symptoms from various organs including the airways and is caused by exposure to chemical substances (2–5). There are no objective methods to demonstrate MCS, considered to be a psychogenic disorder (6).

In previous provocation tests, we found that patients with odour sensitivity complained at provocation with perfume, even when they were unable to smell it, which contraindicates a purely olfactory stimulation (7,8). Patients with odour sensitivity react more strongly with cough than do healthy individuals and asthmatics to provocation with capasaicin inhalation (1). The capsaicin inhalation is an objective test, as has been demonstrated in a controlled study (9). The induced cough can be blocked by local anaesthetics (9), which supports the hypothesis that chemical stimulation of sensory nerve endings, probably the C-fibres of the trigeminal nerve (10)

Received 25 February 2002, accepted in revised form 28 February 2002.
Correspondence should be addressed to: Mats Bende, MD, PhD, Allergy Centre, Central Hospital, SE 541 85 Skövde, Sweden. Fax: +46 500 43 1658; E-mail: mats.bende@vgregion.se

are involved. The receptor for capsaicin, VR-1, binds capsaicin and other vanilloids, but other substances may also activate it (10,11). Stimulation of this receptor could serve to explain the problems of patients with odour sensitivity. Sensitivity to capsaicin varies among both healthy and sick individuals and is directly related to the degree of odour sensitivity (12). The objectives of the present study were to establish limit values for the capsaicin inhalation test.

MATERIAL AND METHODS

Patients

All adult patients presenting with airway problems who were referred to the Allergy Centre in Skövde during a period of 1 year were included in the study. Exclusion criteria were pregnancy and communication difficulties. The latter included both long travelling distance (more than 1 h travelling time) and communication problems due to language and/or mental state. A total of 143 patients were presented at the Centre during the above period. Of these, 14 patients were excluded due to communication difficulties. By oversight, 3 patients were never asked whether they wanted to take part in the study and were consequently excluded. Therefore, 126 patients—58 men and 68 women—were asked whether they were willing to participate in the study. Of these, 27 patients declined, representing a non-response of 21%. Consequently, 99 patients were studied, 44 men and 51 women between the ages of 18 and 73, with an average age of 34 and 36, respectively. They presented various airway symptoms, schematised in Table 1.

All patients were examined with anamneses, an allergy questionnaire, a skin prick test (sometimes in combination with analysis of specific IgE in serum) and a clinical status. Spirometry and methacholine tests were performed in suspected asthma. An evaluation was made of patients' sensitivity to smelling chemical substances, such as perfumes, cleaning agents, flower scents, tobacco smoke and car exhaust fumes, on a scale of 0–3 (0 = no sensitivity; 1 = mild sensitivity; 2 = moderate sensitivity; and 3 = strong sensitivity) for the upper respiratory airways including the larynx and the lower airways. The maximum score was 6 and the minimum was 0 point. In addition, an evaluation was made in order to determine social effects of sensitivity to odorous substances. The patients were thus classified into five categories: 0 = no social effects; 1 = occasional problems at home, at leisure and at the workplace; 2 = daily problems at work; 3 = intermittent sick leave; and 4 = long-term sick leave or disability pension. The results of allergy tests, the diagnosis and the patients' sensitivity to odours are presented in Table 1. One patient had simple chronic bronchitis, and one chronic sinusitis. Three patients had reflux esophagitis: of these, two were smokers. One patient used an angiotensin II-blocker, and no patients were taking ACE-inhibitors of β-blockers. The controls comprised 73 non-smoking, subjectively healthy volunteers (42 women and 31 men, 17–72 years of age, mean 41 years). The capsaicin test was performed on all patients and healthy controls.

Table 1. Presentation of 95 patients with upper and lower respiratory symptoms at the Allergy Centre during 1 year

	Women (*n* = 51)	Men (*n* = 44)	Total (n = 95)
Sensitivity to odours (mean score, 95% CI)	1.9 [1.49; 2.47]	1.3 [0.81; 1.69]	1.6 [1.31; 1.98]
Social score (mean, 95% CI)	0.7 [0.51; 0.98]	0.5 [0.26; 0.69]	0.6 [0.46; 0.78]
Allergy (%)	27 (53%)	32 (73%)	59 (62%)
Symptoms from upper airways by cold air (%)	4 (8%)	7 (16%)	11 (12%)
Symptoms from lower airways by cold air (%)	13 (25%)	6 (14%)	19 (20%)
Rhinitis with allergy	25 (49%)	30 (68%)	55 (58%)
Rhinitis without allergy	13 (25%)	11 (25%)	24 (25%)
Asthma with inhalation corticosteroids	10 (20%)	6 (14%)	16 (17%)
Asthma without inhalation corticosteroids	6 (12%)	10 (23%)	16 (17%)
Asthma with allergy	10 (20%)	10 (23%)	20 (21%)
Asthma without allergy	6 (12%)	6 (14%)	12 (13%)
Smokers	7 (14%)	3 (7%)	10 (11%)
Previous smokers	7 (14%)	10 (23%)	17 (18%)
Cough	22 (43%)	14 (32%)	36 (38%)
Smokers and previous smokers with cough	3 (6%)	5 (11%)	8 (8%)

The capsaicin inhalation test

The test was initiated with inhalation of 1 ml of normal saline for 6 min, followed by 4 min of rest, as previously described (1). The provocation was not administered during an acute respiratory air infection. For inhalation, a nebuliser was used (Pariboy 36, Paulritzau Pari-werk KG, Starnberg-am-See, Germany). The number of coughs was registered with a tape recorder and counted for 10 min from the start of provocation. Thereafter, the subject was provoked in the same manner with increasing concentrations of capsaicin—0.4, 2.0 and 10 μM in a 1 ml solution. If a subject responded with $\geqslant$70 coughs during one dose, no more capsaicin was administered; however, the counting of coughs continued for 10 min. The limit of 70 coughs to abolish the inhalation of capsaicin was set according to previous experience of what a subject could bear.

Statistics

The cough responses to each dose of capsaicin were compared by paired *t*-test after a logarithmic transposition. The relation between patient symptom score and number of coughs after capsaicin inhalation test was analysed by linear regression. In comparing patients and healthy controls, a 95% confidence interval (CI) was used and the limit for a pathological response to the capsaicin inhalation test was determined. To investigate possible confounders for SHR, a multiple logistic regression was fitted to the data. The following explanatory variables were selected in this model: age, sex, presence of asthma and rhinitis, sensitivity to cold air, smoking, and interactions of these variables. To keep this model as parsimonious and plausible as possible, stepwise selection (forward and backward) procedures were used. The significance level for entry and removal of a variable was set to 5%.

RESULTS

One patient started the provocation with normal saline but was afraid to continue with capsaicin, and three individuals were afraid to undergo the provocation with the highest dose. Therefore, 95 patients were taken through the entire protocol. All controls passed the test. The test itself was harmless and well tolerated, and no serious side-effects were registered.

Both patients and controls coughed more with increasing doses of capsaicin, and there was a statistically significant dose–response relationship for the capsaicin provocation at each dose with a *P*-value of at least <0.001. The effect of capsaicin in the patients by the 2.0 μM capsaicin provocation is shown in Fig. 1. The biphasic appearance indicates that this population consists of two subgroups, one of which seems to be more sensitive to capsaicin than the majority.

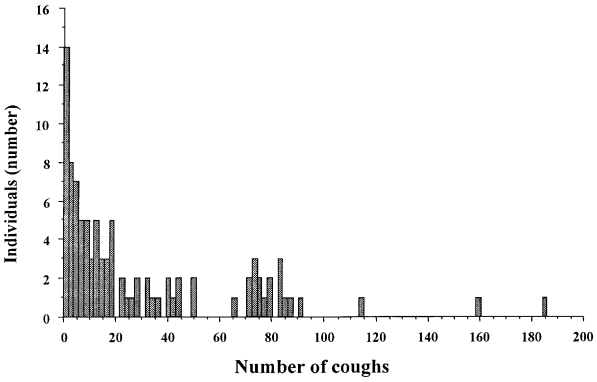

Fig. 1. The distribution of the number of coughs after capsaicin inhalation (2.0 μM) in 95 patients with upper and/or lower airway symptoms. The distribution is bi-phasic, indicating two populations.

There was a direct relationship between the number of coughs and the symptom score of sensitivity to odours (correlation coefficient $r^2 = 0.34$, $P < 0.0001$, capsaicin 2.0 μM). Out of 95 patients, 60 (63%) reported any sensitivity to odours. Patients who exhibited pronounced symptoms, here identified with a total upper and lower airway symptom score of at least 4, were diagnosed with SHR. In total, 15 patients (11 women and 4 men, mean age 42 years old) fulfilled this criteria. The effect of the capsaicin provocation test was then compared between three groups: patients with SHR, patients without SHR and healthy controls (Table 2). Patients with SHR coughed significantly more on capsaicin than the other groups. By studying the mean capsaicin response and the CIs in Table 2 for the healthy controls and patients, the cut-off values for SHR could be approximately 10, 35 and 55 coughs for 0.4, 2.0 and 10 μM capsaicin, respectively (Fig. 2). SHR was related to gender (females), rhinitis and lower airway sensitivity to cold air, but not to age, asthma or smoking.

DISCUSSION

Upper and lower airway complaints from contact with various chemical substances, such as perfumes, cleaning agents, flower scents, car exhaust fumes and tobacco smoke, are common among patients with airway problems who are referred to the Allergy Centre. Epidemiological studies are needed to establish the frequency of this condition in the general population (to be published). In this study, we established three limit values for the capsaicin inhalation test for patients with pronounced sensitivity to odours and symptoms in the upper and lower airways. These patients constitute a clinical population in an allergy centre, thus their symptoms varied greatly. It is necessary to develop a more sophisticated questionnaire to identify patients with SHR,

Table 2. Results of the capsaicin inhalation test, number of coughs (mean and 95% CI), in three groups: patients with SHR, other patients with upper and lower airway symptoms, and healthy controls

		Capsaicin			
Group	*N*	Saline	0.4 μM	2.0 μM	10.0 μM
Patients with SHR	15	5.2[0; 10.5]	32.2 [8.4; 56.0]	70.5 [42.9; 98.2]	83.1 [60.1; 106.2
Other patients	80	0.9 [0.2; 1.6]	10.5 [5.5; 15.4]	21.7 [15.6; 27.8]	41.9 [34.9; 48.8]
Controls	73	0.2 [0; 0.4]	1.3 [0.6; 1.9]	5.6 [3.8; 7.5]	21.2 [17.8; 24.6]

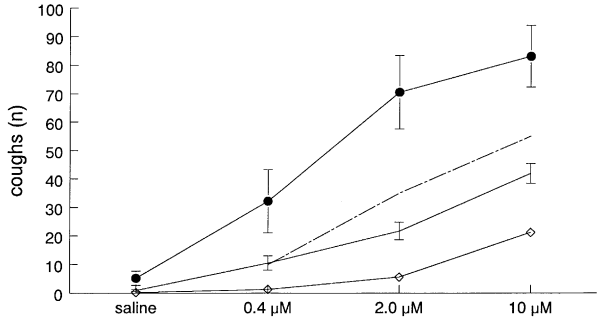

Fig. 2. The mean number of coughs (±SEM) after provocation with saline and three doses of capsaicin in patients with SHR (filled circles, $n = 15$), and others patients without SHR ($n = 80$) and non-smoking healthy subjects (squares, $n = 73$). The dotted line represents the upper limit for a normal capsaicin inhalation test.

one with a combined score of symptoms and social restrictions related to sensitivity to odours.

A study model designed to illustrate the variety of symptoms in large patient groups should be simple and should not require a great deal of time or resources. We feel that our way of carrying out the capsaicin inhalation test meets these requirements and the method has shown good reproducibility (1). We chose to use a common inhalation apparatus that was loaded with a small amount of liquid (1 ml). This produced a large number of particles $> 5\,\mu$M, meaning that a smaller amount of particles dispersed peripherally (13). The limit values that were obtained for a positive capsaicin inhalation test depend on this design and cannot be used directly for inhalation with another inhaler or with different amounts of liquid. In future, it might be possible to use only one concentration of capsaicin. In performing the capsaicin inhalation, saline and lowest dose of capsaicin are likely to be of key importance for training the patient. Discomfort with the capsaicin inhalation may cause patients to change the way they inhale. Certain individuals can avoid coughing to a certain extent, but with a higher concentration the cough reflex becomes irresistible. Therefore, even a low, less irritating dose may be of value for the test.

The degree of sensitivity to capsaicin was positively related to the symptoms induced by chemicals and odours. It must be emphasised that the inhalation test is non-specific, as other patient groups have also shown increased sensitivity to capsaicin (14–18). However, among patients with airway problems who were admitted for allergy exams, we could identify a group of individuals who claimed to be distinctly sensitive to chemical substances such as perfumes, flower scents and tobacco smoke. After provocation of all patients and healthy controls with inhalation of capsaicin, we established limit values for a positive capsaicin inhalation test for patients with SHR. The capsaicin inhalation test is not harmful and can be administered safely to patients with airway problems.

Acknowledgements

The authors are grateful to Birgitta Hallberg, Christel Larsson and Ulla Söderblom for their skilful technical assistance. We would also like to thank all colleagues who helped us with the clinical investigations of the patients. The study was supported by grants from the Regional Health Care Authority of West Sweden.

REFERENCES

1. Millqvist E, Bende M, Löwhagen O. Sensory hyperreactivity — a possible mechanism underlying cough and asthma-like symptoms. *Allergy* 1998; **53:** 1208–1212.
2. Sparks JP, Daniell W, Black DW, *et al*. Multiple chemical sensitivity syndrome: a clinical perspective. *J Occup Med* 1994; **36:** 718–737.
3. Cullen M, Redlich C. Significance of individual sensitivity to chemicals: elucidation of host susceptibility by use of biomarkers in environmental health research. *Clin Chem* 1995; **41:** 1809–1813.
4. Meggs JW, Dunn KA, Bloch RM, Goodman PE, Davidoff AL. Prevalence and nature of allergy and chemical sensitivity in a general population. *Arch Environ Health* 1996; **51:** 275–281.
5. Miller CS. Chemical sensitivity: symptom, syndrome or mechanism for disease? *Toxicology* 1996; **111:** 69–86.
6. Gots RE. Multiple chemical sensitivities—public policy. *Clin Toxicol* 1995; **33:** 111–113.
7. Millqvist E, Löwhagen O. Placebo-controlled challenges with perfume in patients with symptoms suggesting hyperreactive airways. *Allergy* 1996; **51:** 434–439.
8. Millqvist E, Bengtsson U, Löwhagen O. Provocations with perfume in the eyes induce airway symptoms in patients with sensory hyperreactivity. *Allergy* 1999; **55:** 495–499.

9. Millqvist E. Cough provocation with capsaicin is an objective way to test sensory hyperreactivity in patients with asthma-like symptoms. *Allergy* 2000; **55:** 546–550.
10. Caterina M, Schumacher M, Tominaga M, Rosen T, Levine J, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature* 1997; **389:** 816–823.
11. Robbins W. Clinical applications of capsaicinoids. *Clin J Pain* 2000; **16**(Suppl 2): 86–89.
12. Millqvist E. Löwhagen O, Bende M. Quality of life and capsaicin sensitivity in patients with sensory airway hyperreactivity. *Allergy* 2000; **55:** 540–554.
13. Hansson L, Wollmer P, Dahlbäck M, Karlsson JA. Regional sensitivity of human airways to capsaicin-induced cough. *Am Rev Respir Dis* 1992; **145:** 1191–1195.
14. Choudry NB, Fuller RW. Sensitivity of the cough reflex in patients with chronic cough. *Eur Respir J* 1992; **5:** 296–300.
15. Gordon SB, Curran AD, Turley A, *et al*. Glass bottle workers exposed to low-dose irritant fumes cough but do not wheeze. *Am J Respir Crit Care Med* 1997; **156:** 206–210.
16. Fujimura M, Kamio Y, Hashimoto T, Matsuda T. Airway cough sensitivity to inhaled capsaicin and bronchial responsiveness to methacholine in asthmatic and bronchitic subjects. *Respirology* 1998; **3:** 267–272.
17. Doherty MJ, Mister R, Pearson MG, Calverley PM. Capsaicin induced cough in cryptogenic fibrosing alveolitis. *Thorax* 2000; **55:** 1028–1032.
18. Doherty MJ, Mister R, Pearson MG, Calverley PM. Capsaicin responsiveness and cough in asthma and chronic obstructive pulmonary disease. *Thorax* 2000; **55:** 643–649.